SV-BR-1-GM, a breast cancer cell line with features of dendritic cells, induces tumor regression in HLA matched Stage IV breast cancer patients

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ABSTRACT

SV-BR-1-GM is a GM-CSF-engineered breast cancer cell line that expresses HER2, the cancer/testis antigen PRAME, and Class I and Class II HLA antigens. Regression of metastatic breast cancer was seen in clinical trials using irradiated SV-BR-1-GM as a targeted immunotherapy. This is likely attributable to the potentially unique mechanism of action of SV-BR-1-GM. Currently, 29 (edited from submitted abstract stating 28) patients have been inoculated with an SV-BR-1-GM regimen including low-dose cyclophosphamide to reduce immune suppression and local interferon-α2b to boost the response. Confirming previous work, several patients showed regressions. Interestingly, all allele-matched SV-BR-1-GM at ≥ 1 HLA locus. Although derived from a breast cancer cell line, SV-BR-1-GM also resembles dendritic cells and as such may effectively activate breast cancer antigen-specific T cells (*Front Immunol.* 2018; 9:776). Supporting evidence includes:

i) The molecular makeup of SV-BR-1-GM, including the expression of an "immune signature" containing factors such as *IL6*, *IL8*, *KITLG*, and HLA class I and II components such as *HLA-DRA*, *HLA-DRB3*, *HLA-DMA*, *HLA-DMB* and *CD74* (encoding invariant chain and CLIP).

ii) All breast cancer subjects in phase I and IIa clinical trials responding to the SV-BR-1-GM regimen with tumor regression matched with SV-BR-1-GM at least at one HLA allele, particularly at HLA-DRB3.

iii) SV-BR-1-GM cells loaded with a yellow fever virus (YFV) peptide directly activated YFV-specific CD4+ T cells.

iv) The numbers of circulating cancer-associated macrophage-like cells (CAMLs), a bad-prognosis factor, consistently dropped over the course of treatment for patients with tumor regressions.

Despite many clinical trials in different cancer types, little efficacy has been demonstrated for cancer vaccines. The notable positive findings with SV-BR-1-GM may challenge this perspective and suggest that SV-BR-1-GM is a unique, whole-cell targeted immunotherapy with higher efficacy than similar approaches by others, especially in patients matching ≥ 1HLA allele with SV-BR-1-GM.

RESULTS

Potential Mechanisms of Specific Immune Activation in Advanced Breast Cancer by SV-BR-1-GM (Bria-IMT™)

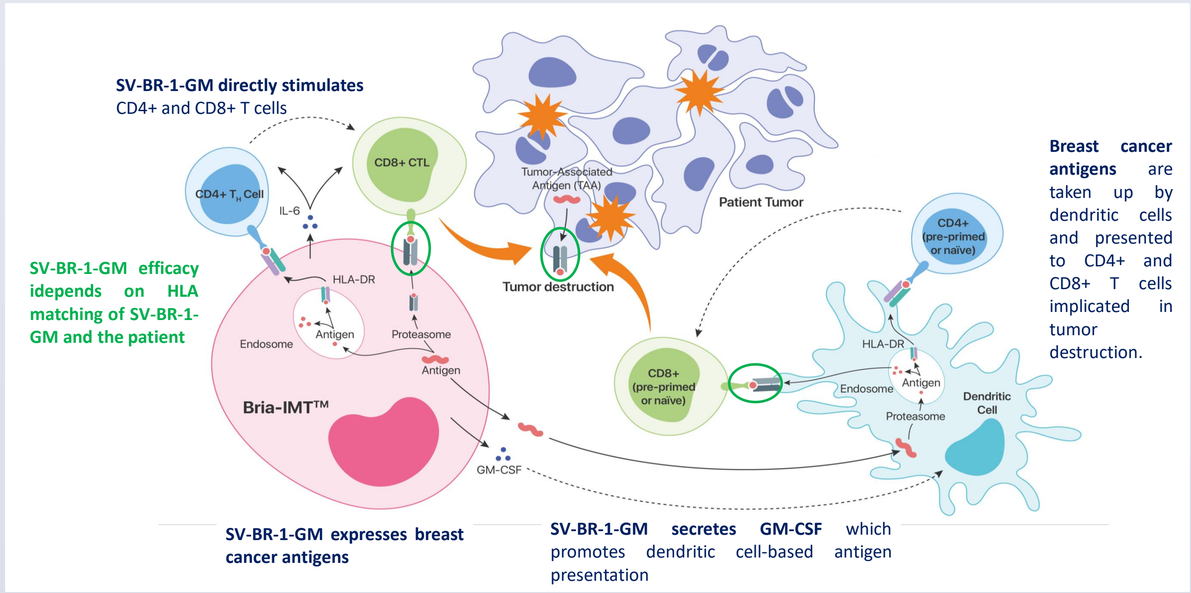

Figure 1. Model of proposed mechanism of action of SV-BR-1-GM (Bria-IMT™). SV-BR-1-GM expresses HLA class I and II and thereby may act as antigen-presenting cells for previously primed T cells. Therefore, in addition to the "classic" cross-presentation mechanism, SV-BR-1-GM may directly activate tumor-targeting CD4+ and CD8+ T cells if the patient and SV-BR-1-GM express identical HLA allele(s). See Lacher et al., 2018 for more information.

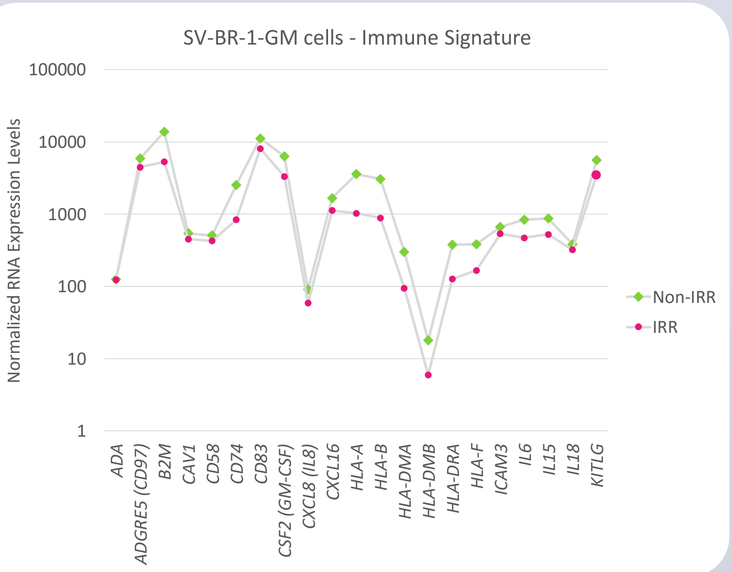

Figure 2. Immune Signature expressed in SV-BR-1-GM (Bria-IMT™). SV-BR-1-GM expresses genes associated with antigen-presenting cells as well as breast epithelial cells. This "Immune Signature" was established based on Illumina microarray data (see Lacher et al., 2018). Here, we have verified it by RNA-Seq.

The blue dots represent non-irradiated SV-BR-1-GM cells while the orange dots represent irradiated **SV-BR-1-GM** cells. Note that the cells are inoculating into patients only after irradiation (10,000-20,000 cGy). IRR, Irradiated (20,000 cGy); Non-IRR, non-irradiated

Table 1. HLA alleles expressed in SV-BR-1-GM

HLA-A Alleles		HLA-B Alleles		HLA-C Alleles		HLA-DRB3 Alleles	
-	24:02	35:08	55:01	04:01	01:02	01:01	02:02

Nomenclature (xx:yy): The first two digits (xx) indicate the allele **group**, both sets of double digits (xx:yy) together the **allele**.

HLA alleles expressed in SV-BR-1-GM. HLA-A, -B, and -DRB3 alleles were determined by a the City of Hope Tissue Typing Laboratory, Duarte, CA. HLA-C alleles were determined using the seq2HLA tool (Boegel et a;., 1012) with FASTQ input data obtained by RNA-Seq on SV-BR-1-GM samples.

SV-BR-1-GM Pilot Phase I (2004-2006):

- Subject A002 had breast cancer that had spread to the lungs, soft tissues and bone
- She initially responded to chemotherapy, but then relapsed with tumor spread to the breast, lungs, soft tissues and bone
- She was treated with the SV-BR-1-GM regimen and had a robust response with substantial tumor regression in the breast and bone, and complete clearance in the lungs and soft tissues
- **Out of 4 evaluable subjects, A002 was the only patient with key HLA matches with SV-BR-1-GM**

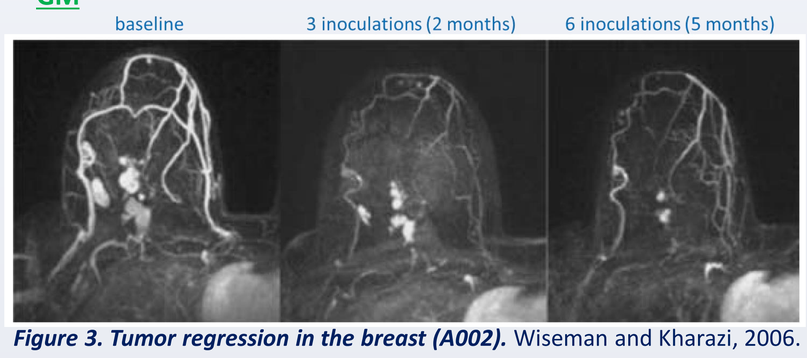

Figure 3. Tumor regression in the breast (A002). Wiseman and Kharazi, 2006.

Additional Clinical Testing in metastatic and locally recurrent breast cancer (2017-current):

- 23 subjects dosed with **SV-BR-1-GM** in phase I/IIa trial (ClinicalTrials.gov NCT03066947**). Study closed for enrollment.**

Patients (n)	HLA Match	Tumor Shrinkage	Biological Response*
5	≥2	40%	60%
18	≥1	22%	39%
9	0	0%	0%

Table 2. Response to SV-BR-1-GM. All subjects with a biological response* (tumor shrinkage and/or CAML reduction) had at least 1 HLA allele match to SV-BR-1-GM. Percentages refer to frequency of response seen.

Circulating Cancer-Associated Macrophage-Like Cells (CAMLs)

CAMLs are giant macrophage-like cells associated with patient tumors and found in the circulation of cancer patients from a variety of cancer types. The presence of tumor markers in CAMLs suggests that CAMLs phagocytose tumor material (Adams et al., 2014). Reduction in CAML frequency following treatment may indicate a favorable prognosis. **Figure 4** indicates that subjects with at least 1 HLA allele match to SV-BR-1-GM tend to respond with reduction in their CAML numbers. Note that PD-L1 expression was seen on CAMLs in 21/23 patients.

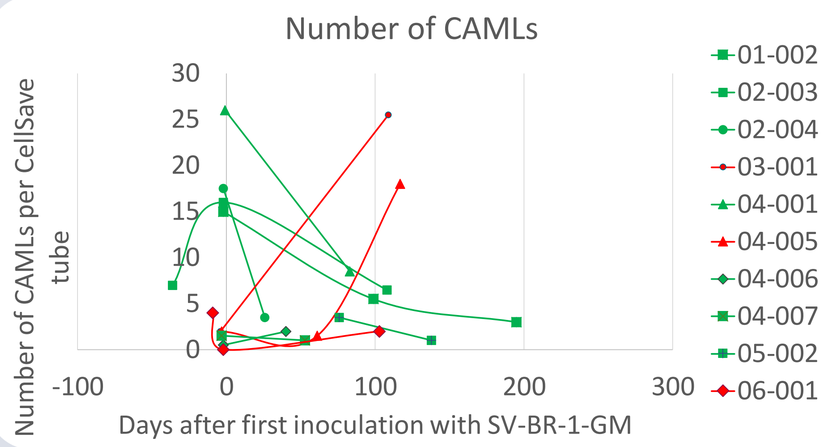

Figure 4. CAMLs following SV-BR-1-GM inoculation. Reduction of CAML numbers in subjects with at least 1 HLA allele match to SV-BR-1-GM (green) compared to mismatching subjects (red). Subjects **01-002** and **05-002** experienced tumor regressions.

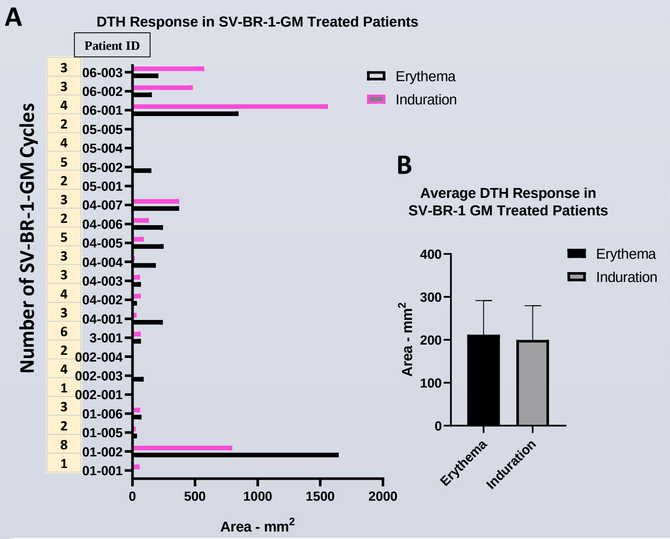

Figure 5: DTH response
Delayed-type hypersensitivity (DTH) is a good marker of cellular (T cell) immune responses. Briefly, for each cycle, SV-BR-1-GM was injected intra-dermally in 4 sites in the upper back and thighs. 2 ±1 days later, these sites were assessed for erythema and induration. **A substantial proportion of patients with follow-up information develop DTH to SV-BR-1-GM, in spite of anergy to test antigens (Candida) in some patients. The most robust response was seen in a patient with regression of multiple pulmonary metastases (01-002).**
A. The largest average response (size) for each patient (induration and corresponding erythema), with largest induration as factor determining which of the 4 inoculation sites is chosen for analysis. Number of cycles next to patient ID.
B. Average of the largest responses (represented in **A**) for all patients.

Conclusions and Outlook

- Tumor regressions and other biological responses most pronounced in subjects with HLA match(es) to SV-BR-1-GM.
- A robust DTH response was elicited by SV-BR-1-GM (Bria-IMT) in most patients
- PD-L1 expression on CAMLs. A combination study of **SV-BR-1-GM** and **pembrolizumab** (anti-PD-1) (ClinicalTrials.gov NCT03328026) is open for enrollment.

Acknowledgements and Contact

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Contact: Markus Lacher (mlacher@briacell.com)

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